REMARKS

Amendments to the Claims

Claims 1, 5, and 7-27 and 29-33 were pending.

Claims 26, 27 and 29-33 were withdrawn from consideration.

Claims 5 and 7-25 have been amended.

Claims 35-42 have been newly added.

Claim 5 and 7-24 have been amended to recite "The protein lattice," instead of "A protein lattice."

Claim 8 has been amended to recite "wherein the linking group fuses the first and second monomers in the protomer at each monomer's terminus to reduce deformation of the monomers and facilitate said alignment of the rotational symmetry axes." Support for Claim 8 can be found in the Specification, for example, at page 9, lines 15-29.

Claim 9 has been amended to better clarify the invention and recite "wherein the protomers are homologous, all protomers in the protein lattice having the same set of monomers." Support for Claim 9 can be found in the Specification, for example, at page 10, lines 9-10; at page 11, lines 28-29; and in Figure 1.

Claim 16 has been amended to recite "wherein the protomers are heterologous, comprising at least two different types of protomers in the protein lattice." Support for Claim 16 can be found in the Specification, for example, at page 13, line 32 through page 14, line 1.

Claim 17 has been amended to recite "wherein the repeating unit comprises protomers of two types, a first type of protomer and a second type of protomer, and wherein each of the two types of protomers has: (1) one monomer from a homologous oligomer assembly consisting of the same type of monomers; and (2) one monomer from a heterologous oligomer assembly consisting of two different types of monomers." Support for Claim 17 can be found in the Specification, for example, at page 16, lines 7-13 and in Figure 2.

Claim 18 has been amended to recite "wherein said first type of protomer in the repeating unit has a first monomer being assembled into said first oligomer assembly that is homologous and said first monomer of the first type of protomer fused to a second monomer which is one of said two different types of monomers of the heterologous oligomer assembly, and wherein said

second type of protomer has a first monomer being assembled into a third oligomer assembly that is homologous and said first monomer of the second type of promoter is fused to a second monomer in the second type of protomer, said second monomer in the second type of protomer being the other of the two different types of monomers of said heterologous oligomer assembly." Support for Claim 18 can be found in the Specification, for example, at page 16, line 29 through at page 17, line 23; and in Figure 2.

Claim 19 has been amended to correct informalities.

Claim 20 has been amended to recite "wherein said third oligomer assembly belongs to a dihedral, tetrahedral or octahedral point group of the same order as said heterologous oligomer assembly." Support for this amendment can be found in the Specification, for example, at page 15, Table 2; page 15, lines 26-32 and Figure 2.

Claim 21 has been amended to recite "said heterologous oligomer assembly belongs to a cyclic point group, wherein one of the rotational symmetry axes of said heterologous oligomer assembly is aligned with the rotational symmetry axes of the first and third oligomer assemblies." Support for this amendment can be found in the Specification, for example, at page 14, lines 15-18; page 15, Table 2; page 15, lines 16-19; page 16, lines 7-28; and Figure 2.

Claim 25 has been amended to recite: "A method of supporting macromolecular entities for x-ray crystallography," instead of "Use of a protein lattice according to claim 1" to reflect the claim language recognized by the U.S. Patent and Trademark Office.

Claims 35-42 has been newly added. Support for these claims can be found in the Specification, for example, at page 18, lines 8-26; and Table 3.

No new matter has been added. Entry of these amendments is respectfully requested.

Examiner Interview

Applicants thank the Examiner, Dr. Jae W. Lee, for granting and conducting the telephone interview on December 18, 2009 with one of the co-inventors, Dr. John Charles Sinclair, and Applicants' Attorneys, David E. Brook and Hak J. Chang. During the interview, Dr. Sinclair explained the differences between the claimed invention and the cited prior art reference, Dotan *et al.*, *Angew. Chem. Int. Ed.*, 1999, 38: 2363-2366 (hereinafter, "Dotan") particularly regarding lack of a rotational symmetry in the tetrahedral assembly of lectin

concanavalin A described in the reference of record, Dotan, as compared to the absolute requirement of such a rotational symmetry of the present invention. To better illustrate the critical differences between the protein lattice of the present invention and that described in Dotan lacking a rotational symmetry, Applicants agreed to submit visual aids to the Examiner. Applicants submit herewith Dr. Sinclair's Declaration under 37 C.F.R. § 1.132 along with the discussed illustrations (Exhibits A-C) demonstrating the difference between the oligomer assembly consisting of four (4) chiral subunits (tetrahedron) of Dotan and an oligomer assembly having 12 subunits consisting of four (4) tetrahedral *point* groups as covered in pending Claim 1 and specifically recited in Claims 10, 12, 19 and 20 of the present Application. In addition, the rejections under 35 U.S.C. § 112 first and second paragraphs were also discussed with respect to the proposed claims. The claim amendments set forth in the present response to the Office Action reflect the discussion held during the interview. The remarks are presented in detail below regarding the rejection under 35 U.S.C. § 102(b) and § 112, first paragraph discussed during the interview. Lastly, Applicants are particularly appreciative of Dr. Lee for granting the phone interview and considering the proposed claim amendments as well as his constructive suggestions and comments.

Rejection of Claims 8 and 16-21 Under 35 U.S.C. § 112, Second Paragraph

Claims 8 and 16-21 have been rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite.

Claim 8 has been rejected for reciting the phrase "relative orientation of the linking group respect to the first and second monomer prior to assembly." Claim 8 has been amended to delete the original phrase and to recite "the linking group fuses the first and second monomers at each monomer's terminus to reduce deformation of the monomers and facilitate said alignment of the rotational symmetry axes."

Claims 16, and Claims 17-21 dependent therefrom, have been rejected for the phrase "the promoters are heterologous with respect to the monomer." Claim 16 has been amended to recite the phrase "the protomers are heterologous, comprising at least two different types of protomers in the protein lattice" to better point out the claimed invention.

Claim 17, and Claims 18-21 dependent therefrom, have been rejected for the phrase "different monomers of the same heterologous oligomer assembly." Claim 17 has been amended to recite "wherein the repeating unit comprises protomers of two types, a first type of protomer and a second type of protomer, and wherein each of the two types of protomers has: (1) one monomer selected from a homologous oligomer assembly consisting of the same type of monomers; and (2) one monomer selected from a heterologous oligomer assembly consisting of two different types of monomers."

Claim 18, and Claims 19-21 dependent therefrom, have been rejected for the phrase "one of said different monomers of the same heterologous oligomer assembly, said heterologous oligomer assembly." Claim 18 has been amend to recite the features of a protein lattice constructed from two different types of protomers (*i.e.*, "heterologous protomers"), each of which having one of two different types of monomers of a heterologous oligomer assembly as clearly illustrated in Figure 2 and described in words at page 13, line 32 through page17, line 30. It is noted that the heterologous oligomer assembly is an oligomer assembly made up of at least two different types of monomers (*e.g.*, bacteriophage T4 gp5 and gp27; *see* the Specification at page 17, lines 1-3; Figure 2).

Rejection of Claims 1, 5 and 7-25 Under 35 U.S.C. § 112, First Paragraph

Claims 1, 5 and 7-25 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description. The Examiner stated that: (1) "...the disclosure of the specification is not read into the claims as a claim limitation and those few examples provided in Figures 1 and 2, and proteins disclosed in Tables 1 and 2 fail to be representative species for the genus of any first and second monomers having essentially any structure"; and (2) " in light of the fact that it is highly unpredictable for one of skill in the art to identify 3-D structure and rotational axes that may exist in any oligomer assemblies comprising any monomer" (*see* the Office Action at page 9, first and second paragraph).

Applicants respectfully traverse this rejection. The written description requirement is met because the present Specification, including the claims originally filed, provides adequate written descriptions so as to indicate Applicants had possession of the genus claim as discussed further below.

According to the Manual of Patent Examining Procedure (MPEP), § 2163 (I), the written description requirement is satisfied where the specification describes the claimed invention in detail so that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). For each claim drawn to a genus, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Regents of the University of California v. Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998). Further, in certain situations, disclosure of even one species can adequately supports a genus. See, *e.g.*, *In re Rasmussen*, 650 F.2d at 1214, 211 USPQ at 326-27. In *Rasmussen*, disclosure of a single method of adheringly applying one layer to another was sufficient to support a generic claim to "adheringly applying" because one skilled in the art reading the specification would understand that it is unimportant how the layers are adhered, so long as they are adhered. *Id.*

Applicants Had Possession of the Claimed Invention

Applicants are entitled to the claimed invention because Applicants had possession of the claimed subject matter as evidenced by the amount of guidance in words and drawings including actual reduction to practice based on laboratory production to the computer illustration for all the aspects of the protein lattice claimed in Claim 1, particularly the structural requirements for the protomers in relation to the oligomer assemblies. The Examiner must consider the entire teachings of the Application, including the claims as originally filed as well as Tables, drawings and illustrations as stated in the MPEP § 2163 (I). Discussed below are various forms of written description in the present Specification which would support Applicants' possession of the genus.

The specification provides sufficient teachings in words, figures (*e.g.*, Figures 1 and 2), and tables (Tables 1-3) to support the genus claim. The Specification provides structural and

functional features common to the members of the genus in words, illustrations and drawings as recited in Claim 1. Briefly, the present application provides written description for the genus of protein lattices created from homologous protomers. Representative species of homologous protein protomers whose resulting protein lattice is illustrated in Figure 1 are tabulated in Table 1. Representative species of heterologous protein protomer whose resulting protein lattice is illustrated in Figure 2 created from heterologous protomers are provided in Table 2. Applicants provide an actual reduction to practice in the Specification (*see* the Specification at page 21, line 24 through page 22, line 18). Tables 1 and 2 clearly demonstrate various types of homologous and heterologous protomers capable of being assembled into a protein lattice based on their common structural features (*i.e.*, identifying characteristics). Contrary to the statement by the Examiner, these tables exemplify and teach structural requirements common to all protomers of the present invention, both homologous and heterologous. Finally, Table 3 provides examples of various oligomer assemblies that meet the necessary structural requirements of and can be utilized in the present invention. Clearly, Applicants were in possession of the genus.

Even if the Examiner is of opinion that only one species being exemplified in the present application, the Examiner should determine, as in the court of *Rasmussen*, that because the structural information can be easily obtained from publicly available sources (*i.e.*, "in possession of the public") as discussed further in detail below and because one skilled in the art reading the present specification would understand that it is not important what the actual identity of a putative oligomer assembly is, so long as the oligomer assembly meets the requirements recited in Claim 1, the written description requirement for the genus is satisfied.

1. Amount of Written Description in the Specification

The Specification teaches how to build a protein lattice of Claim 1 and all claims dependent therefrom. Page 4, lines 8-19 explains how protein lattices can be designed by selecting appropriate oligomer assemblies which have the requisite rotational symmetries set forth in Claim 1. A protomer made out of at least two monomers of two separate oligomer assemblies are a fundamental building block of the claimed protein lattice as set forth in Claim 1. Page 4, line 26 through page 8, line 3 describes the principles by which the symmetries of the lattice derives from the symmetry of rotational axes of oligomer assemblies whose monomer is

selected for making the protomer which self-assembles into a protein lattice. Page 10, line 4 through page 17, line 30 describes various types of protomers as well as oligomer assemblies which can be implemented in the present invention, whose quaternary structures satisfies a requisite rotational symmetry and whose monomers can be used for making a protomer of the present invention.

Specifically, a protein lattice assembled from homologous protomers is described, for example, at page 10, line 9 through page 13, line 31, including Table 1, in which one complete example of such protein lattice is illustrated in Figure 1. A protein lattice assembled from two different types of protomers ("heterologous protomers") is described at page 13, line 32 through page 17, line 30, including Table 2 and one complete example of such protein lattice is illustrated in Figure 2.

2. Illustrations of Examples Achieved By the Present Invention

As noted above, possession of the genus can be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas... See, *e.g.*, *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998). The Specification provides illustrations of two different types of protein lattices: the unary protein lattices assembled from homologous protomers (*e.g.*, Figure 1; page 10, line 9 through page 13, line 31, including Table 1); and binary protein lattices assembled from heterologous protomers (Figure 2; page 13, line 32 through page 17, line 30, including Table 2). Further, Applicants provide actual reduction to practice by showing laboratory production of a protein lattice illustrated in Figure 1. The Specification at page 21, line 26 through page 22, line 18, describes specific experimental procedures and data for the protein lattice assembled from homologous protomers consisting of a monomer selected from human ferritin heavy chain (HFH) and a monomer selected from *E. coli* PurE. Figure 3 is an EM picture of a protein lattice particle. The Examiner is also reminded that drawings, illustrations and sufficient description in words, discussed above, are evidence supporting constructive reduction to practice ('ready for filing').

3. Submission of a Post-filing Example

In the previous response dated July 21, 2008, Applicants submitted an additional post-filing example which demonstrated creation of yet another protein lattice. The document was filed with the European Patent Office on August 16, 2006 in connection with European Patent Application No. 03753741.2 (now EP Patent No. 1,551,862) which corresponds to the present U.S. Application. The document demonstrated a 3-D regular protein lattice created from a multitude of homologous protomers comprising one monomer selected from a small heat shock protein (SHS) and another monomer selected from the streptavidin/streptag assembly. This example of post-filing success is strong evidence supporting a high level of predictability of the present invention as discussed further below.

The Structural Requirement for the Protein Lattice of the Present Invention

The present invention is based on the principle that oligomer assemblies having an appropriate symmetry can be used to construct a protomer, a plurality of which would self-assemble into a stable protein lattice. The structural requirement of an oligomer assembly is fully recited in Claim 1, which necessitates: (1) a first oligomer assembly having at least three rotational symmetry axes; (2) a second oligomer assembly having a rotational symmetry axis of the same order as one of the at least three rotational symmetry axes of the first oligomer assembly; and (3) the rotational symmetry axis of the second oligomer assembly being aligned with the one of the at least three rotational symmetry axes of the first oligomer assembly when said protomers self-assemble into the lattice (Claim 1). These are common requirements of the structural features shared by all protein lattices of the present invention. The protomer created by fusing with or without a linker of at least two monomers of two separate oligomer assemblies ("first oligomer assembly and second oligomer assembly") would form a lattice.

For example, the first oligomer assembly, as exemplified in Figure 1, is human ferritin heavy chain (HFH) which belongs to an octahedral P_4 point group of order 4. The second oligomer assembly, as exemplified in Figure 1, is *E. coli* PurE which belongs to a dihedral D_4 point group of order 4. Having the same order 4 rotational symmetry in both oligomer assemblies, a protomer made out of fusing one monomer from HFH and another monomer from *E. coli* PurE would naturally form a highly ordered structure of a protein lattice as illustrated in

Figure 1, as long as one of the rotational symmetry axes of the first and second oligomer assembly are aligned with each other when said protomers self-assemble into the lattice.

The first promoter of the protein lattice of Figure 2 comprises a first monomer of a first homologous oligomer assembly, namely *E. coli* dps, which belongs to a tetrahedral point group of order 3. The first monomer of the first protomer in Figure 2 is then fused to a second monomer of the first protomer, which is a monomer of a heterologous oligomer assembly, namely bacteriophage T4 gp5 which has a cyclic point group of order 3. The second protomer comprises a first monomer which is a monomer of a heterologous oligomer assembly, namely bacteriophage T4 gp27. The first monomer of the second protomer is fused to a monomer of a third oligomer assembly, namely human 6-pyruvoyl tetrahydropterin synthase (PTPS) which belongs to a dihedral D3 point group of order 3. All of the oligomer assemblies (*i.e.*, *E. coli* dps; bacteriophage T4 gp5 gp27; and Human PTPS) have a rotational symmetry of order 3. Submitted herewith is Exhibits C, D and E which depict the crystal structures of *E. coli* dps (Exhibit C); bacteriophage T4 gp5 and gp27 (Exhibit D); and Human PTPS (Exhibit E). All these oligomer assemblies are able to align when two types of the heterologous protomers described above assemble into a lattice as shown in Figure 2.

In addition to the examples of various protein lattices discussed above, the Specification teaches the structural and functional features common to the genus throughout the Specification (*see*, the Specification at page 4, line 8 through page 8, line 3; page 10, line 4 through page 16, line 28; and Tables 1 and 2).

Applicants respectfully note that the Examiner's reasoning for rejecting the genus claim is misplaced. The Examiner stated:

> Furthermore, in light of the fact that it is highly unpredictable for one of skill in the art to identify 3-D structure and rotational axes that may exist in any oligomer assemblies comprising <u>any monomers, which includes protein from their amino acid sequence, especially when two monomers that are fused together</u> which may significantly alter the 3-D conformation of each of the two monomers, one of skill in the art would not have recognized that Applicants were in possession of the genus of protein lattices (see below 112 1st rejection under enablement for further discussion on "the unpredictability") (Office Action at page 9, final paragraph; emphasis added).

Unlike the statement by the Examiner, one of ordinary skill in the art would not endeavor to predict 3-D structure from any protein or any oligomer assembly based on the amino acid sequence because one of ordinary skill in the art could simply and readily select potential candidates based on detailed and highly reliable structural information readily obtainable from publicly available resources such as Protein Data Bank (PDB) (*see* the Specification at page 4, lines 13-19: "The Protein Data Bank; H. M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T. N. Bhat, H. Weissig, I. N. Shindayalo & P.E. Bourne; Nucleic Acids Research, 28 pp. 235-242 (2000) which is the single worldwide archive of structure data bank of biological macromolecules, also available through websites such as http://www.rcsb.org"). One of ordinary skill in the art would most certainly take great advantage of the vast amount of structural information and knowledge available from the PDB because it is well known that more than 50,000 protein crystal structures have been registered in the PDB.

Once the structural information of an oligomer assembly is obtained from the source exemplified above, there is a high level of predictability for one of ordinary skill in the art in designing a protomer, especially when each of the monomers in a protomer is essentially employed in its entire length with or without a linker as described in the Specification (*e.g.*, the N-fold fusion between HFH and *E. coli* PurE). This task is routine for molecular biologists or protein chemists specialized in protein design and crystallography. The document submitted in the previous response demonstrating a successful construction of a lattice created from protomers, each of which comprises one monomer selected from a small heat shock protein and another monomer selected from the streptavidin/streptag assembly, is strong evidence of such predictability.

The Examiner stated that:

> Although Applicants argue that the specification describes some examples in Figures 1 and 2, it is noted by the Examiner that the disclosure of the Specification is not read into the claims as a claimed limitation and those few examples provided in Figures 1 and 2, and proteins disclosed in Tables 1 and 2 fail to be representative species for the genus of any first and second monomers having essentially any structure. (Office Action at page 9; emphasis added)

Applicants respectfully point out that the disclosure of the Specification does read into the claims as a claimed limitation. All limitations of present Claim 1 are supported by the Specification through express, implicit and inherent disclosure including text and drawings (*see* MPEP § 2163 (I)(B)). Every aspect or element of Claim 1, and all claims dependent therefrom, is sufficiently described and depicted in drawings so as to reasonably convey that the inventor had possession of the subject matter.

Further, Tables 1 and 2 provide representative species for the genus because they disclose various structural categories of point groups to which the oligomer assemblies of particular monomers belong. For example, Table 1 provides structural categories of point groups of potential oligomer assembly (*e.g.*, p = platonic point group; d = dihedral point group). The platonic point group is well known in the art to include, for example, tetrahedron and octahedron point groups. Applicants strongly emphasize that these groups refer to the point of an oligomer assembly. Table 1 provides structural categories for homologous protomers that conforms with the structural requirements of an oligomer assembly whose monomer is employed in making of protomers described in Table 1 and recited in Claims 1 and 9-15. Similarly, Table 2 provides structural categories for heterologous protomers that conform with the structural requirements recited in Claims 1 and 16-21 for making heterologous protomers. The Examiner is reminded that Applicants are not required to provide written descriptions for every possible species of the present invention, so long as sufficient number of the representative species are provided in the Specification so as to reasonably convey to one ordinary skill in the art to conclude that Applicants had possession of the genus claim at the time of the invention. Here, the common structural features required in the present invention are sufficiently taught and exemplified.

The Examiner stated that Claim 1 is directed to the genus of any first and second monomers having essentially any structure (Office Action at page 9). To the contrary, the protomer recited in Claim 1 does not employ any monomer. It is carefully selected from an oligomer assembly whose structural elements strictly conform with the requirements recited in Claim 1 and exemplified in Table 1 for homologous protomers and in Table 2 for heterologous protomers as noted above. The proteins whose oligomer assemblies conform to such a physical requirement are unique. If an oligomer assembly has the requisite physical attributes, a protomer made from a monomer of such oligomer assembly can function as a building block of the protein

lattice of the present invention. Thus, an oligomer assembly or a monomer thereof is not any protein with any structure as stated by the Examiner.

The Examiner quoted in the Office Action a remark by Applicants in the previous response dated July 23, 2008. The Examiner stated that:

> In support of the Examiner's position, Applicants have stated that "at the time the instant application was filed, laboratory production of a protein lattice in accordance with the present invention had only been demonstrated for the quoted example of human HFH and E. coli PurE...Taken together, the limited disclosure in the specification, i.e., a single protein lattice which can be made using human HFH and E. coli PurE,..one of skill in the art would have recognized that the genus of protein lattices, encompassing widely variant species having essentially any structure, can be used in extremely diverse applications... (Office Action at page 10; emphasis added)

The Examiner's interpretation of Applicants' statement in the previous response is in error. The statement by Applicants does not indicate lack of examples or unpredictability of the art at the time of the invention. Instead, it clearly demonstrates an actual reduction to practice of one representative species which strongly supports possession by Applicants.

Moreover, the Examiner stated that "lack of any experimental data to support the notion that all possible combinations of any monomers having any set of rotational symmetry axes can be fused together to form a protein lattice" (Office Action at page 10, first paragraph). As noted above, the written description requirement does not require Applicants to show actual reduction to practice for all possible combinations of any monomers having any set of rotational symmetry axes. Applicants note that provision of representative examples and recitation of common structural features of the genus in words and drawings satisfies the written description requirement.

Further, the Examiner's statement that "all possible combination of any monomer having any set of rotational symmetry axes can be fused to form a protein lattice" (Office Action at page 10, first paragraph) is simply misplaced. The protein lattice of the present invention is not constructed from a protomer of any two fused monomers having a set of rotational symmetry axes. In the present invention, a rotational symmetry of a monomer is not a requirement. Instead, a rotational symmetry is the requisite element for the oligomer assembly (*i.e.*, (1) a first

oligomer assembly having at least 3 rotational axes of symmetry; (2) a second oligomer assembly having a rotational axis of symmetry with the same order with one of the rotational symmetries of the first oligomer assembly; and (3) the rotational axes of symmetry of the first oligomer assembly and the second oligomer assembly must be aligned when the protomers are assembled into the oligomer assembly). Thus, it is not the rotational symmetry of axes of a monomer that is important. It is the entire oligomer assembly to which the monomer belongs, that must conform with the requirement.

The Examiner also stated that: "In addition, the claimed genus of protein lattices include those that are crystalline." The protein lattice of the present invention is an extremely defined and highly ordered structure because it relies on the protomers' natural affinity to form a most stable conformation, a protein lattice. Oligomer assemblies described in the Specification were selected based on their publicly available crystal structure via the PDB. These proteins had been successfully crystallized and subjected to X-ray diffraction. Further, the Examiner relies on the statements by Giege *et al.* published in 1994, ten years prior to the filing of the present application, which are directed to general X-ray crystallography. Since 1994, the technology involved in X-ray crystallography has drastically improved ranging from the protein expression and purification systems to crystallization and diffraction techniques. The technology culminated at the advent of high throughput protein crystallization processes widely used and practiced at the time the invention was made.

The question of whether the written description requirement has been met depends on whether Applicants have put forth adequate guidance to one of ordinary skill in the art which would reasonable to convey that Applicants had possession of the claimed invention. Applicants provided sufficient guidance on the requisite quaternary structure of the selected oligomer assembly and provided examples of specific oligomer assemblies suitable for making a self-assembling protein lattice. It is clear that Applicants unequivocally had possession of the claimed invention at the time of the invention.

Rejection of Claims 1, 5 and 7-25 Under 35 U.S.C. § 112, First Paragraph

Claims 1, 5 and 7-25 stand rejected under 35 U.S.C. § 112, first paragraph, for lacking enablement. The Examiner stated that: "...the specification, while being enabling for a protein

lattice comprising a fusion protein comprising the human ferritin heavy chain (HFH) and the *E. coli* PurE... does not reasonably provide enablement for any protein lattice having a regular structure with a repeating unit repeating in three dimensions, the repeating unit comprising any protein protomers...The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims" (Office Action, bridging paragraph between pages 12 and 13). Applicants respectfully traverse the rejection.

In the Office Action, the Examiner stated that: "the specification lacks disclosure of how any protein lattices comprising any first and second monomers that are fused together essentially having any structure correlate with a desired function/activity..." (Office Action at page 17). Unlike the statement by the Examiner, one of ordinary skill in the art would *not* have been choosing any monomer with any structure. Nor would one of ordinary skill in the art select any protein based on its amino acid sequence. As elaborated above, it is *not* the structure of the monomer of a protomer that is important. What is important is the structure of the entire oligomer assembly to which the monomer belongs. One of ordinary skill in the art would have mainly, if not entirely, relied on the structural information publicly and readily available from the PDB to choose a potential oligomer assembly that met the structural requirement and employ a monomer of the selected oligomer assembly to design a protomer. Once the accurate structure of an oligomer assembly is ascertained, designing of a protomer using a monomer of such oligomer assembly is routine for molecular biologists or protein chemists who have experience in recombinant DNA technology and the protein expression and purification systems.

The Examiner stated that: "It is noted that the state of the art at the time of the invention acknowledges a high level of unpredictability for [1] making a protein crystal, i.e., a protein lattice, with an expectation that it is X-ray diffraction-quality or [2] predicting the number of rotational symmetry axis of a protein from its amino acid sequence" (Office Action at page 18). This statement is also misplaced. One of ordinary skill in the art would not need to predict the number of rotational symmetry axis of a protein from its amino acid sequence. One of ordinary skill in the art would simply select an oligomer assembly whose structural information (*i.e.*, detailed crystal structure) are already available and obtainable from PDB. Moreover, the

rotational symmetry axis pertains to that of the entire oligomer assembly, not to the monomer of the oligomer assembly or monomer of the protomer.

The Examiner stated that because the intended use of the protein lattice of the present invention is x-ray crystallography based on previous Claim 25, a skilled artisan would recognize that it is highly unpredictable in making and using the scope of the invention as claimed, and it would require undue experimentation to determine which structure, out of infinite number of possible protein lattices, that are crystalline, can be used for X-ray crystallography (see Office Action at page 19). This rejection is in error for the following reasons in addition to the remarks made in the previous responses. Each of the eight factors of *In re Wand,* 858. F2d 731, 737; 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) was discussed in detail in the previous response dated June 9, 2009.

One of ordinary skill in the art would not select any random protein. The oligomer assemblies are selected based on their structural attributes which were readily obtainable at the time of the invention from various public sources. The oligomer assemblies of the present invention must meet the structural requirements as recited in Claim 1. Accordingly, most of them, if not all, had been already crystallized for their individual structures. No undue experimentation was required at the time of the invention to resolve the X-ray crystal structure for the protein lattice constituted from oligomer assemblies that had been previously crystallized and whose structures had been already resolved.

Further, the Examiner's focus on certainty with respect to the protomers which form a claimed protein lattice is misplaced, and does not support the rejection. Enablement does not require "certainty." Enablement requires that a person of ordinary skill in the art be able to make and use the invention without engaging in "undue experimentation" using the teachings of the specification and the knowledge in the art. The test of enablement is not whether any experiment is required, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). The level of predictability in the art was high as discussed above. Further, the Specification provides working examples of various types of protein lattices established from uninary and binary protomers as discussed in detail above.

In summary, it would only take routine experimentation, not undue experimentation, for one of ordinary skill in the art to make and use the claimed invention using the disclosure of

Applicants' specification. Therefore, pending Claims 1, 5 and 7-25 meet the enablement requirement under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1, 5, 7-23 and 25 under 35 U.S.C. § 102(b)

Claims 1, 5, 7-23 and 25 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Dotan. The Examiner stated that: "Dotan et al. teach a three dimensional protein lattice having a regular structure with a repeating unit in three dimension, the repeating unit comprising protein protomer, i.e., tetrameric tetrahedral lectin concanavalin A, wherein each protein protomer comprises at least a first monomer, i.e., a monomeric lectin concanavalin A-1 ("-1" denotes that it is the 1 of 4 tetrameric tetrahedral lectin concanavalin A-1), and a second monomer, i.e., a monomeric lectin concanavalin A-2 ("-2" denotes that it is the 2 of 4 tetrameric tetrahedral lectin concanavalin A-1), fused together, the monomers each being a monomer of an oligomer assembly into which the monomers are assembled for assembly of the protomers into the lattice, and wherein said first monomer is a monomer of a first oligomer assembly, i.e., first tetrameric tetrahedral lectin concanavalin A, which has at least three rotational symmetry axes; and wherein said second monomer is a monomer of a second oligomer assembly having a rotational symmetry axis of the same order as one of the at least rotational symmetry axes of the first oligomer assembly and being aligned with the one of the at least three rotational symmetry axes of the first oligomer assembly when said protomer self-assemble into the lattice. The Examiner refers to the Figure 1 at page 2364 of Dotan. Applicants traverse the rejection entirely.

Applicants submit herewith a Declaration by Dr. John Sinclair, one of the co-inventors in the present application, along with Exhibits illustrating the differences between the assembly in Dotan that is described as "tetrahedral" but does not have rotational symmetry and an assembly of the present invention that does have tetrahedral symmetry and a least three "rotational symmetry axis." Dr. Sinclair's Declaration clearly points out the differences between the prior art and the present invention.

The Examiner stated in the interview summary that "the presence of a rotational symmetry axis in a monomer was not a limitation of claim 1." As evidenced by Dr. Sinclair's Declaration, the present invention does not rely on an individual monomer having a rotational symmetry axis. To the contrary, the structural requirement pertains to the oligomer assembly.

An oligomer assembly of the present invention has a rotational symmetry axis when one rotation around the axis moves one monomer into the position of another, so that the assembly as a whole looks identical after the rotation as demonstrated in Exhibits A, C, D and E submitted herewith.

Dr. Sinclair explains, however, that chirality of a monomer becomes critical in the situation where there is a tetrahedral oligomer assembly that consists of only four (4) chiral monomers as in lectin concanavalin A described in Dotan (*i.e.*, one monomer situated at the top of the other three monomers at the bottom). Dr. Sinclair states that "The lack of rotational symmetry in the chiral monomer situated at the top would inevitably destroy any potential rotational symmetry of the entire tetrahedral oligomer assembly because all the putative rotational symmetry axes of a tetrahedron are at the vertex and they require a rotational symmetry of the molecule(s) situated at the vertex (*i.e.*, "point group")" (*see* Dr. Sinclair's Declaration, section 15). When the "tetrameric tetrahedral lectin concanavalin A-1" is rotated around 120 degrees, each individual protein takes on a different conformation (*see* Exhibits A and B). Therefore, lectin concanavalin A does not meet the express requirement of Claim 1. Accordingly, the Examiner's statement that the "tetrameric tetrahedral lectin concanavalin A-1 meets the requirement of the claims to have a set of rotational symmetry axes extending in three directions" is incorrect.

Dr. Sinclair also states that even the authors in Dotan explicitly acknowledged that tetrameric tetrahedral lectin concanavalin A-1 does not have a rotational symmetry. Dotan explicitly states that lectin concanavalin A-1 is "nearly" tetrahedral (*see* Dotan at page 2364, left col., 3rd paragraph, first sentence), not truly tetrahedral. Further, according to Dr. Sinclair, Dotan states that: "The deviation from the true cubic symmetry is apparently due to absence of a true rotational axis in concanavalin A monomers" (Dotan at page 2365, right col., third paragraph, final sentence). The reason as to why the lack of rotational symmetry in a monomer destroys any potential rotational symmetry as in Dotan is discussed above and elaborated in detail in Dr. Sinclair's Declaration.

In contrast to the lectin concanavalin A of Dotan, the oligomer assembly of the present invention has tetrahedral point groups and 12 subunits ("monomers"), which exhibit four rotational symmetry axes of order 3 (*see* the attached Exhibit A) as evidenced by Dr. Sinclair's Declaration. When rotated 120 degree around an axis, the conformation *E. coli* dps achieves a

symmetry exhibiting an identical conformation to the one prior. As noted above and evidenced by Dr. Sinclair's Declaration, it is evident that "tetrameric tetrahedral lectin concanavalin A-1" of Dotan lacks a rotation symmetry.

Even assuming, *arguendo*, that the tetrahedral assembly of Dotan has a rotational symmetry, the rotational symmetry of the first oligomer assembly does not align with the rotational symmetry of the second oligomer assembly. Dotan explicitly states that: "Cross-linking of 1 by a bismannoside with an appropriate spacer imposing staggered positioning (Figure 1a) will lead to the formation of the computer-modeled diamondlilke three dimensional protein lattice shown in Figure 1B" (Dotan at page 2364, left column; emphasis added). This statement by Dotan is further elaborated in Figure 2, in which the lowest interaction energy is associated with a staggered positioning of two lectin concanavalin As (Figure 2, black arrow in the graph; and third Newman projection from left at the bottom of the graph). Thus, even if one of ordinary skill in the art mistakenly assumes that there is a rotational symmetry in the tetrahedral oligomer assembly of Dotan, such a putative rotational symmetry axis of the two tetrahedral oligomer assemblies does not align with each other in the protein lattice depicted in Figure 1b of Dotan. This presents clear differences in the rule of construction between the lattice described by Dotan and that of the present invention.

In sum, the protein lattice as a whole in the present invention exhibits the symmetries of the oligomer assembly as recited in Claim 1, whereas the prior art protein lattice described by Dotan does not. Due to these fundamental differences in construction, the claimed protein lattice is not anticipated by the self-assembling protein lattice of Dotan.

Double Patenting

Claims 1, 5 and 7-25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-31 and 33 of copending Application No. 11/807,922.

Applicants will consider filing a Terminal Disclaimer, as appropriate, upon notice of otherwise allowable subject matter. This will permit Applicants to assess the rejection in view of the claims as ultimately indicated to be allowable, since it is possible that the claims may change during the course of prosecution.

CONCLUSION

In view of the above amendments and remarks, Applicants requests reconsideration and withdrawal of the rejections made in the Office Action of August 18, 2009. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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